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Citation for published version:

Valdes Hernandez, M, Wilson, KL, Aspray, ES & Wardlaw, J 2013, 'Brain findings associated with iodine deficiency identified by magnetic resonance methods: a systematic review', *Open Journal of Radiology*, vol. 3, pp. 180-195. <https://doi.org/10.4236/ojrad.2013.34030>

Digital Object Identifier (DOI):

[10.4236/ojrad.2013.34030](https://doi.org/10.4236/ojrad.2013.34030)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Open Journal of Radiology

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Brain Findings Associated with Iodine Deficiency Identified by Magnetic Resonance Methods: A Systematic Review

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Received July 15, 2013; revised August 15, 2013; accepted August 23, 2013

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ABSTRACT

Objectives: Iodine deficiency (ID) is a common cause of preventable brain damage and mental retardation worldwide, according to the World Health Organisation. It may adversely affect brain maturation processes that potentially result in structural and metabolic brain abnormalities, visible on Magnetic Resonance (MR) techniques. Currently, however, there has been no review of the appearance of these brain changes on MR methods. **Methods:** A systematic review was conducted using 3 online search databases (Medline, Embase and Web of Knowledge) using multiple combinations of the following search terms: iodine, iodine deficiency, magnetic resonance, MRI, MRS, brain, imaging and iodine deficiency disorders (*i.e.* hypothyroxinaemia, congenital hypothyroidism, hypothyroidism and cretinism). **Results:** Up to May 2013, 1673 related papers were found. Of these, 29 studies confirmed their findings directly using MR Imaging and/or MR Spectroscopy. Of them, 28 were in humans and involved 157 subjects, 46 of whom had primary hypothyroidism, 97 had congenital hypothyroidism, 3 had endemic cretinism and 11 had subclinical hypothyroidism. The studies were small, with a mean relevant sample size of 6, median 2, range 1 - 35, while 14 studies were individual case reports. T1-weighted was the most commonly used MRI sequence (20/29 studies) and 1.5 Tesla was the most commonly used magnet strength (6/10 studies that provided this information). Pituitary abnormalities (18/29 studies) and cerebellar atrophy (3/29 studies) were the most prevalent brain abnormalities found. Only fMRI studies (3/29) reported cognition-related abnormalities but the brain changes found were limited to a visual description in all studies. **Conclusions:** More studies that use MR methods to identify changes on brain volume or other global structural abnormalities and explain the mechanism of ID causing thyroid dysfunction and hence cognitive damage are required. Given the role of MR techniques in cognitive studies, this review provides a starting point for researching the macroscopic structural brain changes caused by ID.

Keywords: Iodine Deficiency; MRI; Brain; Hypothyroidism

1. Introduction

Iodine is an important micronutrient and a fundamental substrate for the synthesis of thyroid hormones [1,2]. Tri-iodothyronine (T3) and thyroxine (T4) are examples of iodinated thyroid hormones essential for several cellular metabolic processes and the development of the central nervous system [3]. Thyroid hormone functions are impaired by iodine deficiency [4], reflected as increased

plasma thyroid stimulating hormone (TSH) and plasma T3 concentrations with reduced tissue and plasma T4 levels [5].

Iodine deficiency (ID) is one of the three key micronutrient deficiencies highlighted as major public health issues by the World Health Organisation: in 1990, 1.6 billion people, or 28.9% of the global population, were at risk and it was thus considered a serious public health issue throughout the world [6-8]. In 2011 this figure had

risen to 2 billion and, after starvation, ID is currently the single greatest cause of preventable mental retardation and brain damage [9]. European countries are usually assumed to be iodine sufficient, however, several pockets of insufficiency have been described (including UK, Italy, Belgium), with no official data available for several countries.

The degree of neurological impairment and the likelihood of its permanence are not only related to the severity of ID but also to the stage of life at which the individual is exposed to it [10]. Iodine deficiency disorders, such as hypothyroidism, may reflect a maternal, fetal or neonatal childhood thyroid hormone insufficiency [11]. At differing time-points, thyroid hormones have particular effects on brain maturation, regulation of neuronal development and microglial proliferation [12], dendritic arborisation, synaptogenesis, cell migration and myelination [11]. Fetal's thyroid hormones rely on iodine supplemented from the maternal circulation so as to ensure adequate mental development [13]. Iodine insufficiency in fetal life and early childhood is associated with decreased IQ even in the absence of manifest hypothyroidism [14]. Many studies in areas of mild iodine deficiency have shown a range of developmental impairments including poor visual-motor performance and motor skills, decreased neuromotor and perceptual ability and lower developmental and intelligence quotients [7]. There is clearly an association between sub-optimal intellectual performance and iodine deficiency including maternal iodine deficiency during pregnancy [7,14-18].

Despite recommendations to increase daily iodine intake from 150 µg/day to 250 µg/day during pregnancy, up to 40% of pregnant women in Scotland have been shown to be at risk of iodine deficiency [19]. Although few people have frank iodine deficiency and diet-driven hypothyroidism, a low or marginal intake will present a potential hazard in pregnancy, when demand is increased [20]. Iodine is obtained mainly through the diet. The iodine content of food and water is dependent on a variety of factors: including geographical location, mineral content of the soil, bacteria, rainfall, altitude and fertilisers used [21] as well as longstanding fortification programmes with iodine-supplemented salt introduced to counteract dietary deficiency [22,23]. There is no ongoing iodine-fortification programme in the UK [24]. Main sources of iodine in the British diet are milk and dairy products, and fish and seafood [25]. It is likely that a substantial proportion of the young female population excludes at least one of these food groups from their diets, leading to either low or marginal iodine intake [16]. Meanwhile, fast-food meals and pre-cooked dishes do not ensure that the minimum iodine requirement is fulfilled: 150 - 300 µg I per day [26]. The most recent survey conducted in the UK revealed a median urinary io-

dine excretion (*i.e.* marker of ID at population level) of 80 µg/L, indicative of mild deficiency (50 - 99 µg/L) [9].

The brain is particularly sensitive to the adverse effects of ID since neural development occurs at a critical period, prior to the rest of the body [27]. This is reflected in the disproportionate weight of the brain in a neonate, representing 10% of total body mass, compared to 2% in a fully grown adult [27]. Animal models of ID have provided evidence of changes to the morphology and cytoarchitecture of the brain. In sheep models of ID, reduced brain DNA and brain weight with delayed cerebellar maturation were identified [28-30]. In rat brains studies have reported altered metabolic activity and laminar volumes in the hippocampus and dentate gyrus [31] and altered tissue distribution of other trace elements [32-34]. It is also suggested that certain brain proteins may be down-regulated in particular brain regions [35], anterior commissure axons and mRNA expression may be reduced [36,37], dendrite size may be altered [38] and premature cell apoptosis may result [39]. Additionally, ID may cause a reduction in cerebellar cell size and decreased myelination throughout the Central Nervous System [40].

Magnetic Resonance (MR) is a powerful, non-invasive tool for detecting and quantifying structural and metabolic brain changes in life over time. Although access is limited in some regions, it is increasingly available throughout the world. Despite the strong link between iodine insufficiency and neurodevelopment and impaired cognition, brain structural changes have rarely been investigated in the context of iodine insufficiency. We hypothesise that insufficient dietary iodine intake or aberrant iodine metabolism results in structural and metabolic neurological changes in the brain that can be assessed by MR methods. Currently, few reports exist regarding the appearance of these changes on MR. Studies in ID disorders report histological, psychological, physical and behavioural changes but use no brain MR confirmation and brain changes are often inconsistently described. This systematic review was necessary to clarify reported changes on brain MR.

2. Aims and Hypothesis

2.1. Aims

This review aims to identify what brain structural and metabolic abnormalities related to ID are documented using Magnetic Resonance Imaging (MRI) and other MR techniques such as Magnetic Resonance Spectroscopy (MRS).

2.2. Hypothesis

The hypothesis of this review is that insufficient dietary

iodine content or aberrant iodine metabolism results in structural and metabolic neurological changes in the brain, detectable on MR methods.

3. Methods

3.1. Search Criteria

Primary research studies, published in full and using MR techniques to determine brain region modifications, were identified in a literature search. A combination of case reports, prospective and retrospective studies were reviewed. The electronic search was conducted up to May 2013 using the following databases: Medline[®], Web of Knowledge[®] and Embase[®]. It was supplemented by hand-searching reference lists of the review papers and by request to the corresponding authors of identified papers not openly accessible. Multiple combinations of the following search terms were used: iodine, iodine deficiency, iodine deposits, magnetic resonance imaging/MRI, brain, imaging, hypothyroxinaemia, congenital hypothyroidism, hypothyroidism and cretinism. The latter four search terms were proposed as they may be considered as iodine deficiency disorders. Maternal hypothyroxinaemia may result from inadequate iodine intake [41-44] and may cause neurodevelopmental defects. Neonatal hypothyroxinaemia, from postnatal reductions in T4 concentration, but with normal TSH, may occur due to *in utero* iodine insufficiencies [45,46]. Congenital hypothyroidism, caused by maternal and thence fetal hypothyroidism, may, therefore, also result from iodine deficiency, with an incidence of 1:3000 to 1:4000 live births [47,48]. One of the worst consequences of ID and a more severe form of hypothyroidism is endemic cretinism, a condition characterised by neurological deficits, deaf-mutism and spasticity [49-51] that occurs where ID is common in the community.

One reviewer independently carried out the primary literature search, paper selection, duplicate removal and data extraction up to March 2012 and other reviewer extended the search up to May 2013. Three different reviewers assessed a sample of papers for inclusion and helped extract the relevant data on each occasion. Although papers may have passed eligibility checks according to the inclusion/exclusion criteria listed below, full texts were read prior to final rejection of studies.

3.2. Inclusion Criteria

Studies were included which used MR methods to identify brain structural and/or metabolic changes in the brain associated with ID or ID disorders. Inclusion criteria also comprised studies available in English only. Both human and animal studies were included as well as studies from healthy or diseased brains.

3.3. Exclusion Criteria

Studies were excluded if they did not meet the inclusion criteria or were published only as abstracts without full publication available. Studies in which iodine was used therapeutically or as a drug treatment were rejected and studies which involved the injection of radioactive iodine used as a contrast agent for visualising a specific pathology (e.g. thyroid carcinoma) were also excluded. Studies in which hypothyroidism was induced by thyroidectomy or was due to other non-iodine related causes (such as autosomal, goitrogen, steroid consumption, following head trauma, caused by Hashimoto's thyroiditis, stress or autoimmune aetiology) were rejected. Studies on cancer patients or those in which the MR method did not involve studying or imaging the brain (e.g. thyroid scintigraphy) were also rejected. The literature search produced many papers which involved non relevant subject areas and/or diseases; diabetes mellitus, multiple sclerosis, epilepsy, Parkinson's, Alzheimer's, bipolar disorder and Turner's syndrome are examples which were excluded as the non-iodine related consequences of these diseases may affect the appearance of brain changes. Reviews which discuss MR changes associated with iodine deficiency were excluded from the data analysis unless they included new data that was not published elsewhere. If the cause of the disorder (e.g. hypothyroidism) was not ID or not stated the study was rejected.

3.4. Data Extraction

For each study that was included: the type of MR confirmation, the appearance on MR method, the location of the abnormality, the pathology/disease studied and the sample size (*i.e.* number of subjects) was independently extracted. Often the particular type of MR technique used was not discussed in the body of the text and so the relevant information was extracted from MR image descriptions. Additionally, information related to subject pathology was sometimes acquired from tables.

3.5. Data Analysis

The techniques used to identify structural and/or metabolic brain changes were quantified, including:

Number of subjects included in the studies

- How many studies successfully used MR techniques to determine brain changes
- How many studies that used MR methods reported discrepancies on the brain changes
- Whether the studies included blinding, randomisation or an inclusion/exclusion criteria

Moreover, two further questions were posed:

- Where are the most common locations of the brain changes?

- What diseases/pathologies discussed in the studies were associated with which brain changes/ MR abnormality appearances?

However, these last two questions are not the main focus of this review since results only encompass studies which used MR confirmation, rather than all of the literature that discusses the relationship between iodine deficiency and the brain.

4. Results

The literature search identified 1673 publications; 553 from Medline, 625 from Web of Knowledge, 490 from Embase and 5 from review paper reference lists. 29 of these studies were included in the review (**Table 1** and

Figure 1). 1155 papers were rejected because the paper involved non-relevant diseases [Exclusion Criteria], was not related to the effects of ID on the brain and/or used iodine as a contrast medium or therapy, the full paper was not written in English (*i.e.* no translation was available for 330 papers) or was not attainable through the search databases. Further 60 duplicate papers were rejected. Of the remaining 128, 46 review articles and 47 that did not confirm findings using MR techniques (*i.e.* used CT, Nuclear Medicine methods and/or ultrasound) or those in which the MR technique was not applied to the brain, such as thyroid or whole body scintigraphy, were excluded from the data analysis. Finally, six studies on hypothyroidism that did not specify the cause [Exclu-

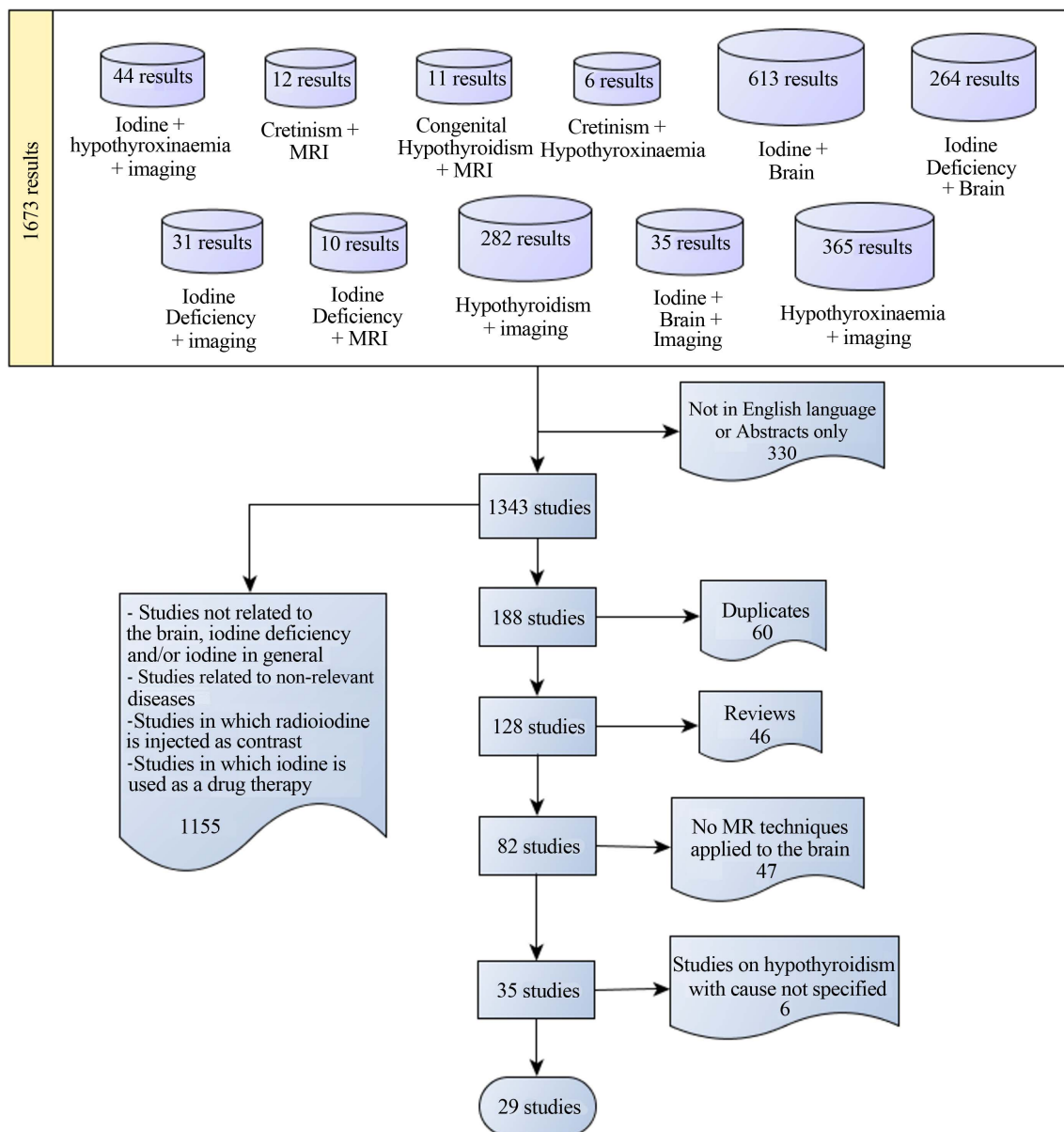


Figure 1. Flow chart summarising the spectrum of results from the literature search.

Table 1. Summary of included studies (Agrawal 2011 to Zhu 2006).

Reference	Pathology studied	Sample type	Relevant Sample size *	MR method	MR sequence /modality	Finding/appearance on MR	Abnormality location	Magnetic field strength
Agrawal 2011 ⁶⁶	PH	Human	1	MRI	T1W + T2W	Enlargement	Pituitary	/
Aijing 2010 ⁵²	PH	Human	8	MRI	/	Enlargement	Pituitary	/
Akinci 2006 ⁶⁷	CH	Human	8	MRS + MRI	T1W +T2W	Decreased NAA/Cr ratios	PWM + Thalamus	1.5T
Alves 1989 ⁶⁸	CH	Human	1	MRI	T2W (spin echo and inversion recovery)	Patchy hyperintensities in white matter	Splenium and Frontal lobe	0.5T
Ashley 2005 ⁵³	PH	Human	1	MRI	T1W	Enlargement	Pituitary	/
Atchison 1989 ⁶⁵	PH	Human	3	MRI	/(images show T1W seq)	Enlargement	Pituitary (sellar and suprasellar)	/
Blasi 2009 ⁶⁹	CH	Human	15	fMRI + MRI	T1W + T2W	Decreased sup. + inf. parietal cortex activation; increased SMA, precentral gyrus, insula + L somatosensory parietal cortex activation	Parietal cortex, SMA, precentral gyrus, insula	1.5T
Dedov 1994 ⁵⁴	PH	Human	10	MRI	Spin-echo	Empty sella turcica (on 6/10 subjects)	Pituitary	0.234T
Desai 1996 ⁷⁰	CH	Human	10	MRI	T1W + T2 * W (gradient echo) on selected patients	Enlargement	Pituitary	0.2T
Dutta 2012 ⁶⁴	PH	Human	1	MRI	T1W	Empty sella turcica	Pituitary	/
Ehirim 1998 ⁵⁵	PH	Human	1	MRI	T1W	Enlargement	Pituitary	/
Garcia-Centeno 2010 ⁵⁶	PH	Human	13	MRI	T1W	Empty sella turcica	Pituitary	1.5T
Goswami 1999 ⁵⁷	PH	Human	1	MRI	T1W	Enlargement	Pituitary	/
Graber 2009 ⁷¹	CH	Human	1	MRI	T1W	Hypoplasia	Cerebellar vermis	/
Gupta 2005 ⁷²	CH	Human	5	MRS + MRI	STEM, T1W + T2W	Increased Cho/Cr ratio Mild cerebral cortical atrophy in frontal and parietal lobes	/	2T
Hasegawa 2010 ⁸⁰	PerH	Rat	8	MRI	/	Reduced total brain volume but ratio of hippocampal volume to total brain volume remains constant	Brain as a whole	7T
Kroese 2004 ⁵⁸	PH	Human	1	MRI	/	Enlargement	Pituitary	/
Lee 2008 ⁵⁹	PH	Human	1	MRI	T1W + T2W	Enlargement	Pituitary	/
Mauceri 1997 ⁷³	CH	Human	1	MRI	T2W	Hypoplasia	R. cerebellar vermis & hemisphere	/
Fujiwara 2008 ⁷⁴	CH	Human	6	MRI	/	Decreased anterior pituitary, ectopic posterior pituitary (on 4/6 subjects)	Pituitary	/
Passeri 2011 ⁶⁰	PH	Human	1	MRI	T1W	Enlargement	Pituitary	/
Sengupta 2012 ⁶³	PH	Human	1	MRI	T1W	Enlargement (hyperplasia)	Pituitary	/
Shogan 2010 ⁶¹	PH	Human	1	MRI	T1W	Sella turcica expansion with pituitary enlargement	Pituitary	/
Tai 1993 ⁷⁸	EC	Human	3	MRI	T1W + T2W	Altered intensity	Globus Pallidus + Substantia Nigra	/

Continued

Tajima 2007 ⁷⁵	CH	Human	1	MRI	/	Atrophy	Cerebellum	/
Wheeler 2011 ⁷⁶	CH	Human	35	MRI	T1W + T2W	Decreased L. hippocampal size	Hippocampus	1.5T
Wheeler 2012 ⁷⁷	CH	Human	14	fMRI	T1W	Increased bilateral activation	Hippocampus	1.5T
Young 1999 ⁶²	PH	Human	2	MRI	/	Enlargement	Pituitary	/
Zhu 2006 ⁷⁹	SH	Human	11	fMRI + MRI	T1W + T2W	Decreased activation	IFG, DLPFC + SMA	1.5T

sion Criteria] were excluded from the main data analysis and discussed separately.

4.1. Sample Size

In total, 165 subjects were included from the 29 studies. Of these, 46 subjects were in studies on primary hypothyroidism [52-66] (*i.e.* in which hypothyroidism was related to ID), 97 subjects in studies on congenital hypothyroidism [67-77], 3 subjects in a study of endemic cretinism [78], 11 subjects in a study of subclinical hypothyroidism [79,80] and 8 subjects in a study of perinatal hypothyroidism [80] (**Figure 2**). One study used animals [80], involving 8 congenital hypothyroid and 8 control rats aged between 7 and 11 months old, yet there was no reporting of death numbers or inclusion/exclusion criteria. The mean sample size (for subjects included in all studies) was 6, the median was 2 and the range 1 - 35, but 14 studies were single case reports [53,55,57-61,63, 64,66,68,71,73,75]. The age range of the human subjects was 0 - 50 years. The study with the largest number of included subjects was from Wheeler *et al.* (2011) [76], with 35 congenital hypothyroid patients.

4.2. Blinding, Randomisation and Inclusion/Exclusion Criteria

The quality of the data presented by this study was assessed following the PRISMA statement [81] and a modification of the QUADAS tool [82]. Results are shown in **Table 2**. Two studies used blinding of assessors to iodine status [69,76], and the image processing on other study [77] was done fully automatically. Although the data processing in all fMRI studies was also done fully automatically, there was no evidence of blindness in the imaging data acquisition. Randomisation was only provided in the animal study whereby rats were randomly assorted into control and treatment groups for MRI experimentation [80]. Ten studies gave implicit inclusion/exclusion criteria through the description of the characteristics of the sample and five gave them explicitly [67,69,74,76,77]. Reasons for rejection were patients with unrelated disorders which may affect cerebral function or development such as chromosomal or metabolic

Number of included subjects with associated diseases/pathologies

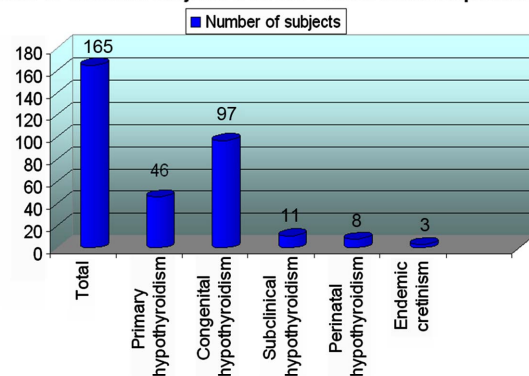


Figure 2. Number of subjects on each pathology included.

disorders, risk factors for brain injury (e.g. hypoxia, teratogens), central nervous system disorders, head trauma, prematurity, congenital malformations or a psychiatric disorder.

4.3. Type of MR Confirmation

The most commonly used imaging method was structural MRI (29/29 studies) (**Tables 1 and 3**), predominantly with conventional structural sequences. MRS was used in 2 studies [67,72] and functional MRI (fMRI) in 3 studies [69,77,79]. T1-weighted (T1W) was the sequence most widely used (in 20/29 studies). T2-weighted (T2W) sequence was utilised in 11/29 studies whilst 6/29 studies did not clarify the MRI sequence used. In 2 studies, only 60% of the hypothyroid patients showed brain changes on MRI [54,74] (**Table 3**).

Only 7 MRI studies utilised contrast enhancement; Gadolinium was used in each of these [55-57,60-62,65]. Both MRS studies [67,72] used shimming techniques and water suppression chemical shift selection pulses but only one study discussed the additional use of Stimulated Echo Acquisition Mode (STEAM) [72].

None of the 29 included papers investigated the effect of using different MR magnetic field strengths on the appearance of brain changes caused by ID, with 11/29 of the studies not clarifying the strength used. Most studies used a 1.5 Tesla magnet strength (6/29 studies) with two using a low 0.2 Tesla strength [54,70]. The animal study

Table 2. Study quality and risk of bias.

Referen-ce	Patients blinded	Data collectors blinded	Outcome assessors blinded	Gender balance	Random selection	Sample representative according to the aim of the study	Tests are repeatable	Results can be replicated	Withdrawals from the study explained	Inclusion/ exclusion criteria given
Agrawal 2011 ⁶⁶				1 F	n/a	✓			n/a	n/a (case report)
Aijing 2010 ⁵² (retrospective)	✓			n/s	all cases presented on a centre	✓	✓		n/a	✓
Akinci 2006 ⁶⁷				n/s	n/s	✓	✓	✓	n/a	✓
Alves 1989 ⁶⁸				1 F	n/a		✓		n/a	n/a (case report)
Ashley 2005 ⁵³				1 F	n/a		✓		n/a	n/a (case report)
Atchison 1989 ⁶⁵				2 F 1 M	n/s	✓	✓		n/a	(inclusion only) 3 case reports
Blasi 2009 ⁶⁹			✓	10 F 5 M	all (those consented) identified by neonatal screening	✓	✓	✓	n/a	✓
Dedov 1994 ⁵⁴ (retrospective)	✓			n/s	Included all presented patients (110), given the inclusion criteria		✓		n/a	✓
Desai 1996 ⁷⁰				5 F 5 M	n/s		✓		n/s	
Dutta 2012 ⁶⁴				1 M					n/a	n/a (case report)
Ehirim 1998 ⁵⁵				1 M		✓			n/a	n/a (case report)
Garcia Centeno 2010 ⁵⁶ (retrospective)	✓			2 M 11 F	Included all presented patients (56), given the inclusion criteria		✓	n/a	n/a	✓
Goswami 1999 ⁵⁷				1M			✓		n/a	n/a (case report)
Graber 2009 ⁷¹				1 F			✓		n/a	n/a (case report)
Gupta 2005 ⁷²				n/s			✓			n/s
Hasegawa 2010 ⁸¹	✓	✓	✓	Equal M and F	✓		✓	✓		✓
Kroese 2004 ⁵⁸				1 F	n/a		Conventional exam		n/a	n/a (case report)
Lee 2008 ⁵⁹				1 F	n/a		Conventional exam.		n/a	n/a (case report)
Mauceri 1997 ⁷³				1 M	n/a	✓	Conventional exam.		n/a	n/a (case report)
Fujiwara 2008 ⁷⁴				3 M 3 F	Screened all patients born 2000-2004	✓	✓		n/a	✓
Passeri 2011 ⁶⁰				1 F		✓	Conventional exam.		n/a	n/a (case report)
Sengupta 2012 ⁶³				1F		✓	✓		n/a	n/a (case report)

Continued

Shogan 2010 ⁶¹		1F			n/a	n/a (case report)
Tai 1993 ⁷⁸		3 M			n/a	n/a (case report)
Tajima 2007 ⁷⁵		1 M	✓	Conventional exam.	n/a	n/a (case report)
Wheeler 2011 ⁷⁶	✓	14 M 21 F	✓	✓	n/a	✓
Wheeler 2011 ⁷⁷	Computational assessment	n/s	✓	✓	n/a	✓
Young 1999 ⁶²		3 F	✓	Conventional exam.	n/a	n/a (case report)
Zhu 2006 ⁷⁹		10 F 1 M	n/s	✓	4 n/s	Inclusion criteria only

used a high strength 7 Tesla magnet [80]. Other magnet strengths were used by 1 study each: 0.5 Tesla [68] and 2 Tesla [72].

4.4. Pathologies Associated with Brain Abnormalities

Several studies of ID investigated brain changes in the context of a particular disease, with 27/29 studying changes in pathological brains. In the animal study, transient perinatal hypothyroidism was induced by anti-thyroid drug methimazole and so, although mimicking the consequences of ID, the rat brains were considered as non-diseased [80]. Zhu *et al.* [79] reported subjects with subclinical hypothyroidism and so the brains of these individuals were considered non-pathological since they did not have the overt form of the disease. Brain changes were seen on MR in all studies in the context of certain pathologies: primary, non-autoimmune hypothyroidism (15/29 studies), congenital hypothyroidism (11/29 studies), perinatal hypothyroidism (1/29 studies), endemic cretinism (1/29 study), subclinical hypothyroidism (1/29 studies) (**Figure 2**).

Primary hypothyroidism was most commonly associated with pituitary enlargement/hyperplasia (13/15 studies) whilst congenital hypothyroidism was related most strongly with cerebellar atrophy/hypoplasia (**Figure 3** and **Table 3**).

4.5. Location of the Abnormalities

Thirteen out of 29 studies (32 subjects) reported homogenous diffuse enlargement of the pituitary gland and/or pituitary hyperplasia [52,53,55,57-63,65,66,70]. Several (7/29) also described suprasellar extension with compression of the optic chiasm; both features which mimic those of a suprasellar tumour. However, 4 other studies discussed empty sella turcica syndrome (*i.e.* absence of the diaphragm sella, reduced hypophysis volume and extension of the intrasellar subarachnoid region) [54,56,

Brain changes most commonly associated with particular diseases / pathologies

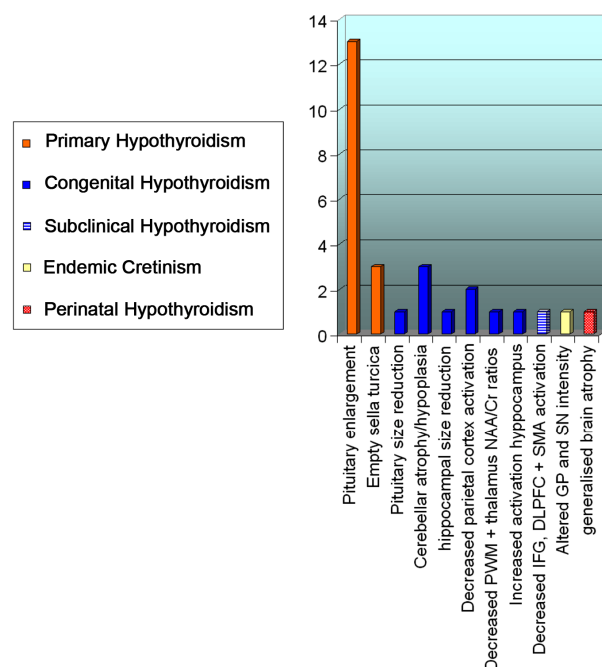


Figure 3. Studied imaged brain abnormalities in the context of a particular disease/pathology. This bar chart shows the brain abnormalities most commonly associated with particular disease/pathologies (caused by iodine deficiency) for the included studies.

64] and a decrease in anterior pituitary size combined with an ectopic posterior pituitary [74].

After the pituitary gland, the cerebellum was the next most cited location for brain abnormalities (**Table 3**) on 3 case studies of congenital hypothyroid subjects [71,73, 75], which reported abnormal cerebellar structure [71] and hypoplasia [71,73] or atrophy [75]. These findings suggest ID may contribute to aberrant development of the cerebellar hemispheres and vermis [73] or be associated with mechanisms that lead to regional atrophy [71,75].

Table 3. Appearance of brain abnormalities in the context of specified diseases, on the MRI methods and sequences utilised, for the included studies. The number of studies that reported differently the abnormality appearance on the same disease and using the same MR method specified (*i.e.* contradictory results) is also recorded.

Disease	MR method	MR sequence	Number of studies using MR method and sequence	Abnormality appearance on the MR method and sequence	Number of studies reporting contradictory results using the same method (not necessarily using the same sequence)
CH	MRI	No specific sequence stated	2	Decreased anterior pituitary, ectopic posterior pituitary ⁷⁴ (4/6 patients)	1 study of CH reported pituitary enlargement on 10/10 patients ⁷⁰
				Cerebellar atrophy, intact brainstem and thin corpus callosum ⁷⁵ (case study)	0
				Pituitary enlargement ⁷⁰ (10/10 patients)	1 study of CH reported decreased pituitary size on 4/6 patients ⁷⁴
		T1W	3	Cerebellar vermis hypoplasia, 4 th ventricle enlargement and abnormal cerebellar structure ⁷¹ (case study)	0
				Decreased L. hippocampal size ⁷⁶ (35/35 patients)	0
				Hyperintense frontal lobe white matter ⁶⁸ (case study)	0
	fMRI (+MRI)	T2W	2	R. cerebellar vermis & hemisphere hypoplasia ⁷³ (case study)	0
				1 study reported decreased sup. + inf. parietal cortex activation; increased SMA, precentral gyrus, insula + L somatosensory parietal cortex activation ⁶⁹ (15/15 patients)	1 study reported increased bilateral activation in the hippocampus ⁷⁷ (14/14 patients), controls activated only left hippocampus. Not necessarily a contradictory result because studies' (refs 69 and 77) aims and tasks were different
		T1W + T2W	2	Decreased NAA/Cr ratios in PWM + thalamus ⁶⁷ (8/8 patients)	1 study of CH reported increased Cho/Cr ratio without stating any specific brain area on 5/5 patients ⁷²
				Increased Cho/Cr ratio (no specific brain area stated), normal white matter and mild cortical atrophy in frontal and parietal lobes ⁷² (5/5 patients)	1 study of CH reported decreased NAA/Cr ratios in PWM + thalamus on 8/8 patients ⁶⁷
PH	MRI	T1W + T2W	2		
		T2W	1	Pituitary enlargement (1/1 patient, case study) ⁶⁶	3 studies of PH reported empty sella turcica on 20/24 patients in total ^{54,56,64}
		No specific sequence stated, but figures showed T1W structural scans	5	Pituitary enlargement ^{52,58,62} (Presented on 11/11 patients in total. Persisted in 2/11 patients after treatment)	
				Empty sella turcica ^{54,56} (total: 19/23 patients)	12 studies of PH reported pituitary enlargement on 22/22 patients ^{52,53,55,57-63,65,66}
		T1W	12	Pituitary enlargement ^{53,55,57,59,60,63,65, 66} (all case studies. Total: 10 patients)	3 studies of PH reported empty sella turcica on 20/24 patients in total ^{54,56,88}
				Sella turcica expansion with pituitary enlargement ⁶¹ (case study)	0
EC	MRI	T1W	1	Hyperintense Globus pallidus + substantia nigra ⁷⁸ (3/3 patients)	0
		T2W	1	Hypointense Globus pallidus + substantia nigra ⁷⁸ (3/3 patients)	0
PerH	MRI	Sequence not specified	1	Reduced total brain volume but ratio of hippocampal volume to total brain volume remains constant ⁸⁸ (8/8 animals)	0
SH	fMRI (+MRI)	T1W + T2W	1	Decreased activation in the IFG, DLPFC + SMA ⁷⁹ (11/11 patients)	0

Two studies found abnormalities in the hippocampus [76,80]: Wheeler *et al.* [76] found that the left hippocampus specifically was reduced in size in 35 patients with congenital hypothyroidism, whereas Hasegawa *et al.* [80] found that, although the hippocampal volume was decreased in mammals with perinatal hypothyroidism, this reduction did not affect the hippocampal to brain volume ratio and so was merely part of generalised brain atrophy. One fMRI study found increased bilateral activation in the hippocampus of 14/14 congenital hypothyroid patients, in contrast with 15/15 controls in which increased activation was only observed in the left hippocampus [77] during a visuospatial memory task.

Tai *et al.* [78] found that three ID patients all showed Sylvian fissure enlargement and abnormal signal intensity in the globus pallidus and substantia nigra on different MRI methods (*i.e.* hyperintense on T1W and hypointense on T2W). These structures are very metabolically active and contain large amounts of iodine [83] and so may be more susceptible to insults caused by ID. Additionally, Alves *et al.* [68] found hyperintense white matter in the anterior and posterior forceps, splenium and frontal lobes on T2W MRI.

The two MRS studies included obtained different results despite studying the same disease: one found increased Cho/Cr ratio and no change in the NAA/Cr ratio but did not specify the brain area affected [72]; the other discovered decreased NAA/Cr ratios in the parietal white matter and thalamus and no Cho/Cr ratio abnormalities [67].

Blasi *et al.* [69] used fMRI to show that 15 congenital

hypothyroid patients had greater activation in the bilateral supplementary motor area, the opercular area of the precentral gyrus, the left somatosensory parietal cortex and the corresponding insula whilst control subjects had greater activation in the superior parietal cortex when performing a mental rotation task. Congenital hypothyroid patients also deactivated the inferior parietal cortex to a greater extent than controls. Zhu *et al.* [79] used fMRI analysis on 11 patients and found that euthyroid patients activated five regions of interest when performing the task but that subclinical hypothyroid subjects only activated 2/5 of these regions (bilateral parietal areas and bilateral premotor areas) [79]. The blood oxygen level dependant response was not seen in the middle/inferior frontal gyri, bilateral dorsolateral prefrontal cortex or supplementary motor area/anterior cingulate cortex suggesting that the frontal cortex is thus an area of abnormality and that working memory may be affected in iodine deficient subjects [79].

4.6. Geographical Area of the Population Studied in Different Studies

Studies from 10 countries contributed data to this review: India (6 studies), USA (6 studies), China (4 studies), Italy and Japan (Hokkaido prefecture) (3 studies each), Canada (2 studies) and The Netherlands, Spain, Russia and Turkey (1 study each) (**Figure 4**). From these countries, only Italy and Russia are known to have mild to moderate iodine deficiency in 2011 [84] (based on median urinary iodine level: UIC from 20 to 99 µg/L).

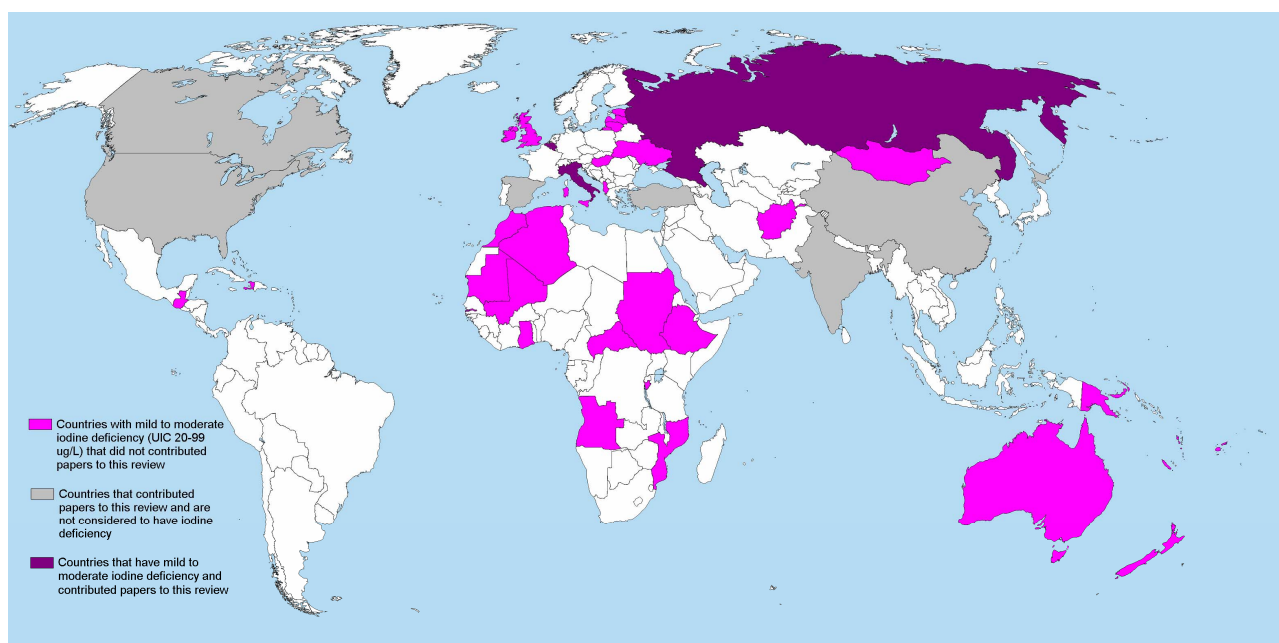


Figure 4. Map showing the countries that have mild to moderate iodine deficiency based on median urinary iodine concentration (UIC) as reported in 2011 by Andersson *et al.*, 2012 [84] and those from which data contributed to this review.

However, publications from India, Turkey and China refer ID as a health issue in some regions. In terms of sample size, the majority of the data analysed by this review corresponds to studies from Canada (not considered to have ID) and from the northern region of Japan: known as having high iodine intake (UIC more than 300 µg/L [84]), on a study that screened 83232 neonates, reported symptoms of ID related disease in 47 and confirmed it in 6 [74].

5. Discussion

Iodine deficiency results in metabolic and/or structural brain alterations which are detectable on MR imaging techniques. Of the papers identified as potentially relevant, only 29/82 confirmed the presence of the brain changes by applying MR techniques, as the majority of studies in this field rely on histochemical findings as depicting structural brain changes. Six studies on hypothyroidism (ID related disorder) were excluded as ID was not explicitly stated as the cause of the disease [Exclusion criteria]. However, 3 of them use, in addition to MRI, a nuclear medical imaging technique: Positron Emission Tomography (PET) [85,86] and Single Photon Emission Computed Tomography (SPECT) [87]. This indicates that the spectrum of medical imaging techniques applied to study brain changes associated with ID related disorders is wide.

Although thyroid disorders related to ID can produce identifiable structural brain abnormalities, these can be highly inconsistent (**Table 3**). Despite the prevalence of pituitary abnormalities (identified by 17/29 studies), this finding was highly contradictory (enlargement was reported in 32 subjects whilst size reduction or empty sella in 30). Cerebellar and hippocampal abnormalities were, however, consistently reported throughout few of the studies included, acknowledged by others [6,7] and found in animals [29,30,40,80]. Nevertheless, the majority of the studies included in this review overlooks basic structural brain changes (e.g. global or regional atrophy) and were limited to visual regional descriptions. MRI was used in most of the studies included in this review; which was dominated by research in the context of primary and congenital hypothyroidism, both in terms of the number of studies and the subject sample size.

Despite the recognized impact of ID in human health, the low prevalence of ID disorders in the general population may have incidence in the lack of large-sized studies evaluating structural brain changes in this condition. The median sample size was 5, as many of the included studies are single case reports. Including studies which encompassed iodine deficiency disorders rather than ID alone would have increased the scope of the review, but could also have meant that other non-iodine related consequences of these diseases may have affected the ap-

pearance of the brain changes. Several of the case studies also often presented no methods sections and so MRI acquisition methods and statistical analysis methods may have been inadequate. With little evidence of statistical analysis, the significance of structural brain abnormalities/changes may have been unreliable; these brain structure sizes could actually be considered within the normal range if not compared with acceptable control brain scans. Additionally, representative images were frequently presented in these case studies, increasing selection bias since researchers were not blinded to case/control status.

Blasi *et al.* [69] and Wheeler *et al.* [76] were the only included studies from which utilised researcher blinding. However, these studies are inclined to create other assumptions. Blasi *et al.* [69] uses the siblings of the congenital hypothyroid patients as control subjects, who may also have been affected by iodine ID in the environment and so may be predisposed to brain changes that have not yet manifested clinically or are not yet visible on MRI. Blasi *et al.* [69] additionally used fMRI along with a mental rotation task. The differences in blood oxygen level dependant response activation between cases and controls may be due to hypothyroid patients disengaging from the task rather than activating different, resultant brain areas [88] and there is also no guarantee in fMRI that subjects are performing the task as intended rather than thinking of other, irrelevant information, thus activating non-task dependent brain areas. Wheeler *et al.* [76] stated that the MRI data acquired from 'unacceptable' scans was disregarded and the measurements from subjects in the same group and of the same age and gender were used instead. The researchers did not clarify how many scans were deemed inappropriate and they did not provide brain scan exclusion criteria specifically and so again, selection bias is prevalent. It also assumes that the disregarded scans would have been similar to those of the other subjects.

Many studies were conducted to ascertain the effects of levothyroxine therapy in hypothyroid patients (*i.e.* whether brain abnormalities seen on MR could be reversed with this treatment). Since these are not directly related to the effects of ID, dependability becomes more disputable. Other sources of inconsistency include the use of differing field strengths among several studies (ranging from 0.2T to 7T) and specific MR sequences are also not always provided. Pituitary hyperplasia is often confused with pituitary adenomas [55,62]. Hence, a consistent field strength which adequately displays these differences on MR images is necessary. In the study by Akinci *et al.* [67], researchers performed a whole body MRI scan; the clarification of small brain structure details may have been improved by using a head coil. Several studies also did not detail the time-frame between

repeat MRI scans and so differences between studies in terms of time elapsed could increase result discrepancies.

Tai *et al.* [78] discuss the brain changes found as being in the areas of the globus pallidus and substantia nigra; hyperintense on T1W and hypointense on T2W. However, no distinction is given as to the degree of hyper- or hypo-intensity for which an appropriate grading scale consistent across all studies is required. The research in this paper could also have been improved by the additional utilisation of Computed Tomography (CT) scans in all subjects; this would enable authors to determine whether the change in intensity was due to calcifications and thus prevent assumptions.

To the best of our knowledge, there has not been a systematic review before on the appearance of brain changes on MR caused by iodine deficiency. Despite the large worldwide availability of MR techniques and the importance of the study of iodine insufficiency, given its strong link with neurodevelopment and impaired cognition, most current literature on ID reports histological and cytoarchitectural brain alterations only, with no MR confirmation. In some countries known as having mild to moderate ID the major causes of the disorders included in this review are immunological or iatrogenic rather than ID (e.g. United Kingdom). Therefore this review, rather than reflecting the spectrum of ID related brain abnormalities provides guidance and constitutes a call for future studies in ID and brain health.

Strengths of this work include searching multiple databases over a large time-frame, the use of comprehensive search terms, the inclusion of fMRI and MRS studies, the inclusion of ID diseases rather than research discussing ID alone, the inclusion of both human and animal studies and the inclusion of healthy and diseased brains. A weakness, however, is the exclusion of non-English papers.

The literature on brain structural and metabolic abnormalities related to ID that are documented using MR methods is limited to few studies with differing field strengths and MR sequences, small sample sizes and poor evidence of blinding, randomisation and an inclusion/exclusion criteria in many of them. Interobserver bias also affects some of the included studies; for example, in the study by Hasegawa *et al.* [80] (the only included study that uses randomisation) volumetric analysis of the hippocampus was manually performed by one researcher only. Additionally, the limited description of the signal changes (when mentioned) lacks from an adequate (*i.e.* normalised) grading, all of which attempts against the scope of the results obtained.

6. Directions for Future Research

More studies are required which correlate histological findings with MR image results and the utilisation of

more standardised sequences and field strengths are necessary. With the increased focus on the consequence of iodine insufficiency both *in utero* and in infancy, it is important to understand the brain structural modifications caused by ID, given that neurodevelopmental and cognitive outcomes range in severity according to the level and timing of ID. Future work should include global and regional atrophy changes to identify directions for the research that will improve the understanding of the pathophysiological mechanisms related with the effects of ID in the brain.

7. Acknowledgements

This work was mainly funded by the College of Medicine and Veterinary Medicine of the University of Edinburgh, with partial funds from Row Fogo Charitable Trust and SINAPSE (Scottish Imaging Network A Platform for Scientific Excellence) collaboration. Funds from the Royal Society of Edinburgh, NESTA (National Endowment for Science, Technology and the Arts) and The Scottish Funding Council through the Scottish Crucible initiative are also gratefully acknowledged.

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Acronyms and Abbreviations for Tables

PH: Primary Hypothyroidism;
 CH: Congenital Hypothyroidism;
 EC: Endemic Cretinism;
 PerH: Perinatal Hypothyroidism;
 SH: Subclinical Hypothyroidism;
 R: right; L: left;
 NAA: N-acetylaspartate;
 Cr: Creatinine; Cho: Choline;
 sup: Superior; inf: Inferior;
 PWM Parietal White Matter;
 IFG: Inferior Frontal Gyrus;
 DLPFC: Dorsolateral Prefrontal Cortex;
 SMA: Supplementary Motor Area;
 T1W: T1-weighted sequence;
 T2W: T2-weighted sequence